<110> Hong Jin et al.

<120> Recombinant RSV Expression Systems and
  Vaccines

<130> 7682-045

<140> 09/161,122
<141> 1998-09-25

<160> 47

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caaaaaaatg gggcaaataa gaatttgata agtaccactt aaatttaact   50

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ctagagttaa atttaagtgg tact   24

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tatcaaattc ttatttgccc cattttttg gtttatgcaa gtttgttgta                50

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cgcatttttt cgcgtaatat gcgtcggtac                                     30

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gtattcaatt atagttatta aaaattaaaa atcatataat tttttaaata               50

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acttttagtg aactaatcct aaagttatca ttttaatctt ggaggaataa               50

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<400> 8
atttaaaccc taatctaatt ggtttatatg tgtattaact aaaattacgag              50

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<400> 9
atattagttt ttgacacttt ttttctcgtt atagtgagtc gtatta                  46
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2

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agcttaatac gactcactat aacga                                                25


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gaaaaaaagt gtcaaaaact aatatctcgt aatttagtta atacacatat                     50


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<213> Artificial Sequence

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aaaccaatta gattagggtt taaatttatt cctccaagat taaaatgata                     50


<210> 13
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<400> 13
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<220>
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gtttaacacg tggtgag   17

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<400> 16
acatataggc atgcacc   17

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gcaaaatgga tcccatt   17

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tggttggtat accagtgt   18

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<400> 19
taccaagagc tcgagtca   18

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<223> Primer

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<400> 21   20
tttaccatat gcgctaatgt

<210> 22
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<400> 22   19
acgcgaaaaa atgcgtaca

<210> 23
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<400> 23   18
acgagaaaaa agtggcaa

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<400> 24   17
ctcaccacgt gttaaac

<210> 25
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5

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ggtgcatgcc tatatgt                                                      17
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<210> 26
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aatgggatcc attttgtcc                                                    19
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<400> 27
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aacactggta taccaacca                                                    19
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<210> 28
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<213> Artificial Sequence

<220>
<223> Primer

<400> 28
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<211> 2165
<212> PRT
<213> Virus

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            20                  25                  30
Ser Tyr Ile Phe Asn Gly Pro Tyr Leu Lys Asn Asp Tyr Thr Asn Leu
        35                  40                  45
Ile Ser Arg Gln Asn Pro Leu Ile Glu His Met Asn Leu Lys Lys Leu
    50                  55                  60
Asn Ile Thr Gln Ser Leu Ile Ser Lys Tyr His Lys Gly Glu Ile Lys
65                  70                  75                  80
Leu Glu Glu Pro Thr Tyr Phe Gln Ser Leu Leu Met Thr Tyr Lys Ser
                85                  90                  95
Met Thr Ser Ser Glu Gln Ile Ala Thr Thr Asn Leu Leu Lys Lys Ile
            100                 105                 110
Ile Arg Arg Ala Ile Glu Ile Ser Asp Val Lys Val Tyr Ala Ile Leu
        115                 120                 125
```

```
Asn Lys Leu Gly Leu Lys Glu Lys Asp Lys Ile Lys Ser Asn Asn Gly
    130                 135                 140
Gln Asp Glu Asp Asn Ser Val Ile Thr Thr Ile Ile Lys Asp Asp Ile
145                 150                 155                 160
Leu Ser Ala Val Lys Asp Asn Gln Ser His Leu Lys Ala Asp Lys Asn
                165                 170                 175
His Ser Thr Lys Gln Lys Asp Thr Ile Lys Thr Thr Leu Leu Lys Lys
            180                 185                 190
Leu Met Cys Ser Met Gln His Pro Pro Ser Trp Leu Ile His Trp Phe
        195                 200                 205
Asn Leu Tyr Thr Lys Leu Asn Asn Ile Leu Thr Gln Tyr Arg Ser Asn
    210                 215                 220
Glu Val Lys Asn His Gly Phe Thr Leu Ile Asp Asn Gln Thr Leu Ser
225                 230                 235                 240
Gly Phe Gln Phe Ile Leu Asn Gln Tyr Gly Cys Ile Val Tyr His Lys
                245                 250                 255
Glu Leu Lys Arg Ile Thr Val Thr Thr Tyr Asn Gln Phe Leu Thr Trp
            260                 265                 270
Lys Asp Ile Ser Leu Ser Arg Leu Asn Val Cys Leu Ile Thr Trp Ile
        275                 280                 285
Ser Asn Cys Leu Asn Thr Leu Asn Lys Ser Leu Gly Leu Arg Cys Gly
    290                 295                 300
Phe Asn Asn Val Ile Leu Thr Gln Leu Phe Leu Tyr Gly Asp Cys Ile
305                 310                 315                 320
Leu Lys Leu Phe His Asn Glu Gly Phe Tyr Ile Ile Lys Glu Val Glu
            325                 330                 335
Gly Phe Ile Met Ser Leu Ile Leu Asn Ile Thr Glu Glu Asp Gln Phe
            340                 345                 350
Arg Lys Arg Phe Tyr Asn Ser Met Leu Asn Asn Ile Thr Asp Ala Ala
            355                 360                 365
Asn Lys Ala Gln Lys Asn Leu Leu Ser Arg Val Cys His Thr Leu Leu
    370                 375                 380
Asp Lys Thr Val Ser Asp Asn Ile Ile Asn Gly Arg Trp Ile Ile Leu
385                 390                 395                 400
Leu Ser Lys Phe Leu Lys Leu Ile Lys Leu Ala Gly Asp Asn Asn Leu
            405                 410                 415
Asn Asn Leu Ser Glu Leu Tyr Phe Leu Phe Arg Ile Phe Gly His Pro
            420                 425                 430
Met Val Asp Glu Arg Gln Ala Met Asp Ala Val Lys Ile Asn Cys Asn
    435                 440                 445
Glu Thr Lys Phe Tyr Leu Leu Ser Ser Leu Ser Met Leu Arg Gly Ala
    450                 455                 460
Phe Ile Tyr Arg Ile Ile Lys Gly Phe Val Asn Asn Tyr Asn Arg Trp
465                 470                 475                 480
Pro Thr Leu Arg Asn Ala Ile Val Leu Pro Leu Arg Trp Leu Thr Tyr
                485                 490                 495
Tyr Lys Leu Asn Thr Tyr Pro Ser Leu Leu Glu Leu Thr Glu Arg Asp
            500                 505                 510
Leu Ile Val Leu Ser Gly Leu Arg Phe Tyr Arg Glu Phe Arg Leu Pro
            515                 520                 525
Lys Lys Val Asp Leu Glu Met Ile Ile Asn Asp Lys Ala Ile Ser Pro
    530                 535                 540
Pro Lys Asn Leu Ile Trp Thr Ser Phe Pro Arg Asn Tyr Met Pro Ser
545                 550                 555                 560
His Ile Gln Asn Tyr Ile Glu His Glu Lys Leu Lys Phe Ser Glu Ser
                565                 570                 575
Asp Lys Ser Arg Arg Val Leu Glu Tyr Tyr Leu Arg Asp Asn Lys Phe
            580                 585                 590
```

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```
Asn Glu Cys Asp Leu Tyr Asn Cys Val Val Asn Gln Ser Tyr Leu Asn
        595                     600                     605
Asn Pro Asn His Val Val Ser Leu Thr Gly Lys Glu Arg Glu Leu Ser
        610                     615                     620
Val Gly Arg Met Phe Ala Met Gln Pro Gly Met Phe Arg Gln Val Gln
625                     630                     635                 640
Ile Leu Ala Glu Lys Met Ile Ala Glu Asn Ile Leu Gln Phe Phe Pro
                645                     650                     655
Glu Ser Leu Thr Arg Tyr Gly Asp Leu Glu Leu Gln Lys Ile Leu Glu
                660                     665                     670
Leu Lys Ala Gly Ile Ser Asn Lys Ser Asn Arg Tyr Asn Asp Asn Tyr
                675                     680                     685
Asn Asn Tyr Ile Ser Lys Cys Ser Ile Ile Thr Asp Leu Ser Lys Phe
        690                     695                     700
Asn Gln Ala Phe Arg Tyr Glu Thr Ser Cys Ile Cys Ser Asp Val Leu
705                     710                     715                 720
Asp Glu Leu His Gly Val Gln Ser Leu Phe Ser Trp Leu His Leu Thr
                725                     730                     735
Ile Pro His Val Thr Ile Ile Cys Thr Tyr Arg His Ala Pro Pro Tyr
                740                     745                     750
Ile Gly Asp His Ile Val Asp Leu Asn Asn Val Asp Glu Gln Ser Gly
                755                     760                     765
Leu Tyr Arg Tyr His Met Gly Gly Ile Glu Gly Trp Cys Gln Lys Leu
        770                     775                     780
Trp Thr Ile Glu Ala Ile Ser Leu Leu Asp Leu Ile Ser Leu Lys Gly
785                     790                     795                 800
Lys Phe Ser Ile Thr Ala Leu Ile Asn Gly Asp Asn Gln Ser Ile Asp
                805                     810                     815
Ile Ser Lys Pro Ile Arg Leu Met Glu Gly Gln Thr His Ala Gln Ala
                820                     825                     830
Asp Tyr Leu Leu Ala Leu Asn Ser Leu Lys Leu Leu Tyr Lys Glu Tyr
        835                     840                     845
Ala Gly Ile Gly His Lys Leu Lys Gly Thr Glu Thr Tyr Ile Ser Arg
        850                     855                     860
Asp Met Gln Phe Met Ser Lys Thr Ile Gln His Asn Gly Val Tyr Tyr
865                     870                     875                 880
Pro Ala Ser Ile Lys Lys Val Leu Arg Val Gly Pro Trp Ile Asn Thr
                885                     890                     895
Ile Leu Asp Asp Phe Lys Val Ser Leu Glu Ser Ile Gly Ser Leu Thr
                900                     905                     910
Gln Glu Leu Glu Tyr Arg Gly Glu Ser Leu Leu Cys Ser Leu Ile Phe
        915                     920                     925
Arg Asn Val Trp Leu Tyr Asn Gln Ile Ala Leu Gln Leu Lys Asn His
        930                     935                     940
Ala Leu Cys Asn Asn Lys Leu Tyr Leu Asp Ile Leu Lys Val Leu Lys
945                     950                     955                 960
His Leu Lys Thr Phe Phe Asn Leu Asp Asn Ile Asp Thr Ala Leu Thr
                965                     970                     975
Leu Tyr Met Asn Leu Pro Met Leu Phe Gly Gly Gly Asp Pro Asn Leu
                980                     985                     990
Leu Tyr Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu Thr Glu Ala
                995                     1000                    1005
Ile Val His Ser Val Phe Ile Leu Ser Tyr Tyr Thr Asn His Asp Leu
        1010                    1015                    1020
Lys Asp Lys Leu Gln Asp Leu Ser Asp Asp Arg Leu Asn Lys Phe Leu
1025                    1030                    1035                1040
Thr Cys Ile Ile Thr Phe Asp Lys Asn Pro Asn Ala Glu Phe Val Thr
                1045                    1050                    1055
```

8

```
Leu Met Arg Asp Pro Gln Ala Leu Gly Ser Glu Arg Gln Ala Lys Ile
              1060              1065              1070
Thr Ser Glu Ile Asn Arg Leu Ala Val Thr Glu Val Leu Ser Thr Ala
              1075              1080              1085
Pro Asn Lys Ile Phe Ser Lys Ser Ala Gln His Tyr Thr Thr Thr Glu
              1090              1095              1100
Ile Asp Leu Asn Asp Ile Met Gln Asn Ile Glu Pro Thr Tyr Pro His
1105              1110              1115              1120
Gly Leu Arg Val Val Tyr Glu Ser Leu Pro Phe Tyr Lys Ala Glu Lys
              1125              1130              1135
Ile Val Asn Leu Ile Ser Gly Thr Lys Ser Ile Thr Asn Ile Leu Glu
              1140              1145              1150
Lys Thr Ser Ala Ile Asp Leu Thr Asp Ile Asp Arg Ala Thr Glu Met
              1155              1160              1165
Met Arg Lys Asn Ile Thr Leu Leu Ile Arg Ile Leu Pro Leu Asp Cys
              1170              1175              1180
Asn Arg Asp Lys Arg Glu Ile Leu Ser Met Glu Asn Leu Ser Ile Thr
1185              1190              1195              1200
Glu Leu Ser Lys Tyr Val Arg Glu Arg Ser Trp Ser Leu Ser Asn Ile
              1205              1210              1215
Val Gly Val Thr Ser Pro Ser Ile Met Tyr Thr Met Asp Ile Lys Tyr
              1220              1225              1230
Thr Thr Ser Thr Ile Ser Ser Gly Ile Ile Ile Glu Lys Tyr Asn Val
              1235              1240              1245
Asn Ser Leu Thr Arg Gly Glu Arg Gly Pro Thr Lys Pro Trp Val Gly
              1250              1255              1260
Ser Ser Thr Gln Glu Lys Lys Thr Met Pro Val Tyr Asn Arg Gln Val
1265              1270              1275              1280
Leu Thr Lys Lys Gln Arg Asp Gln Ile Asp Leu Leu Ala Lys Leu Asp
              1285              1290              1295
Trp Val Tyr Ala Ser Ile Asp Asn Lys Asp Glu Phe Met Glu Glu Leu
              1300              1305              1310
Ser Ile Gly Thr Leu Gly Leu Thr Tyr Glu Lys Ala Lys Lys Leu Phe
              1315              1320              1325
Pro Gln Tyr Leu Ser Val Asn Tyr Leu His Arg Leu Thr Val Ser Ser
              1330              1335              1340
Arg Pro Cys Glu Phe Pro Ala Ser Ile Pro Ala Tyr Arg Thr Thr Asn
1345              1350              1355              1360
Tyr His Phe Asp Thr Ser Pro Ile Asn Arg Ile Leu Thr Glu Lys Tyr
              1365              1370              1375
Gly Asp Glu Asp Ile Asp Ile Val Phe Gln Asn Cys Ile Ser Phe Gly
              1380              1385              1390
Leu Ser Leu Met Ser Val Val Glu Gln Phe Thr Asn Val Cys Pro Asn
              1395              1400              1405
Arg Ile Ile Leu Ile Pro Lys Leu Asn Glu Ile His Leu Met Lys Pro
              1410              1415              1420
Pro Ile Phe Thr Gly Asp Val Asp Ile His Lys Leu Lys Gln Val Ile
1425              1430              1435              1440
Gln Lys Gln His Met Phe Leu Pro Asp Lys Ile Ser Leu Thr Gln Tyr
              1445              1450              1455
Val Glu Leu Phe Leu Ser Asn Lys Thr Leu Lys Ser Gly Ser His Val
              1460              1465              1470
Asn Ser Asn Leu Ile Leu Ala His Lys Ile Ser Asp Tyr Phe His Asn
              1475              1480              1485
Thr Tyr Ile Leu Ser Thr Asn Leu Ala Gly His Trp Ile Leu Ile Ile
              1490              1495              1500
Gln Leu Met Lys Asp Ser Lys Gly Ile Phe Glu Lys Asp Trp Gly Glu
1505              1510              1515              1520
```

9

```
Gly Tyr Ile Thr Asp His Met Phe Ile Asn Leu Lys Val Phe Phe Asn
              1525                  1530                  1535
Ala Tyr Lys Thr Tyr Leu Leu Cys Phe His Lys Gly Tyr Gly Lys Ala
              1540                  1545                  1550
Lys Leu Glu Cys Asp Met Asn Thr Ser Asp Leu Leu Cys Val Leu Glu
              1555                  1560                  1565
Leu Ile Asp Ser Ser Tyr Trp Lys Ser Met Ser Lys Val Phe Leu Glu
         1570                  1575                  1580
Gln Lys Val Ile Lys Tyr Ile Leu Ser Gln Asp Ala Ser Leu His Arg
    1585                  1590                  1595                  1600
Val Lys Gly Cys His Ser Phe Lys Leu Trp Phe Leu Lys Arg Leu Asn
              1605                  1610                  1615
Val Ala Glu Phe Thr Val Cys Pro Trp Val Val Asn Ile Asp Tyr His
         1620                  1625                  1630
Pro Thr His Met Lys Ala Ile Leu Thr Tyr Ile Asp Leu Val Arg Met
         1635                  1640                  1645
Gly Leu Ile Asn Ile Asp Arg Ile His Ile Lys Asn Lys His Lys Phe
      1650                  1655                  1660
Asn Asp Glu Phe Tyr Thr Ser Asn Leu Phe Tyr Ile Asn Tyr Asn Phe
1665                  1670                  1675                  1680
Ser Asp Asn Thr His Leu Leu Thr Lys His Ile Arg Ile Ala Asn Ser
              1685                  1690                  1695
Glu Leu Glu Asn Asn Tyr Asn Lys Leu Tyr His Pro Thr Pro Glu Thr
              1700                  1705                  1710
Leu Glu Asn Ile Leu Ala Asn Pro Ile Lys Ser Asn Asp Lys Lys Thr
      1715                  1720                  1725
Leu Asn Asp Tyr Cys Ile Gly Lys Asn Val Asp Ser Ile Met Leu Pro
      1730                  1735                  1740
Leu Leu Ser Asn Lys Lys Leu Ile Lys Ser Ser Ala Met Ile Arg Thr
1745                  1750                  1755                  1760
Asn Tyr Ser Lys Gln Asp Leu Tyr Asn Leu Phe Pro Met Val Val Ile
              1765                  1770                  1775
Asp Arg Ile Ile Asp His Ser Gly Asn Thr Ala Lys Ser Asn Gln Leu
         1780                  1785                  1790
Tyr Thr Thr Thr Ser His Gln Ile Ser Leu Val His Asn Ser Thr Ser
         1795                  1800                  1805
Leu Tyr Cys Met Leu Pro Trp His His Ile Asn Arg Phe Asn Phe Val
    1810                  1815                  1820
Phe Ser Ser Thr Gly Cys Lys Ile Ser Ile Glu Tyr Ile Leu Lys Asp
1825                  1830                  1835                  1840
Leu Lys Ile Lys Asp Pro Asn Cys Ile Ala Phe Ile Gly Glu Gly Ala
              1845                  1850                  1855
Gly Asn Leu Leu Leu Arg Thr Val Val Glu Leu His Pro Asp Ile Arg
         1860                  1865                  1870
Tyr Ile Tyr Arg Ser Leu Lys Asp Cys Asn Asp His Ser Leu Pro Ile
    1875                  1880                  1885
Glu Phe Leu Arg Leu Tyr Asn Gly His Ile Asn Ile Asp Tyr Gly Glu
    1890                  1895                  1900
Asn Leu Thr Ile Pro Ala Thr Asp Ala Thr Asn Asn Ile His Trp Ser
1905                  1910                  1915                  1920
Tyr Leu His Ile Lys Phe Ala Glu Pro Ile Ser Leu Phe Val Cys Asp
              1925                  1930                  1935
Ala Glu Leu Ser Val Thr Val Asn Trp Ser Lys Ile Ile Ile Glu Trp
         1940                  1945                  1950
Ser Lys His Val Arg Lys Cys Lys Tyr Cys Ser Ser Val Asn Lys Cys
      1955                  1960                  1965
Met Leu Ile Val Lys Tyr His Ala Gln Asp Asp Ile Asp Phe Lys Leu
    1970                  1975                  1980
```

10

```
Asp Asn Ile Thr Ile Leu Lys Thr Tyr Val Cys Leu Gly Ser Lys Leu
1985            1990              1995              2000
Lys Gly Ser Glu Val Tyr Leu Val Leu Thr Ile Gly Pro Ala Asn Ile
            2005              2010              2015
Phe Pro Val Phe Asn Val Val Gln Asn Ala Lys Leu Ile Leu Ser Arg
            2020              2025              2030
Thr Lys Asn Phe Ile Met Pro Lys Lys Ala Asp Lys Glu Ser Ile Asp
            2035              2040              2045
Ala Asn Ile Lys Ser Leu Ile Pro Phe Leu Cys Tyr Pro Ile Thr Lys
        2050              2055              2060
Lys Gly Ile Asn Thr Ala Leu Ser Lys Leu Lys Ser Val Val Ser Gly
2065              2070              2075              2080
Asp Ile Leu Ser Tyr Ser Ile Ala Gly Arg Asn Glu Val Phe Ser Asn
                  2085              2090              2095
Lys Leu Ile Asn His Lys His Met Asn Ile Leu Lys Trp Phe Asn His
            2100              2105              2110
Val Leu Asn Phe Arg Ser Thr Glu Leu Asn Tyr Asn His Leu Tyr Met
            2115              2120              2125
Val Glu Ser Thr Tyr Pro Tyr Leu Ser Glu Leu Leu Asn Ser Leu Thr
        2130              2135              2140
Thr Asn Glu Leu Lys Lys Leu Ile Lys Ile Thr Gly Ser Leu Leu Tyr
2145              2150              2155              2160
Asn Phe His Asn Glu
                2165


<210> 30
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<212> PRT
<213> Virus


<400> 30
Met Asp Pro Ile Ile Asn Gly Asn Ser Ala Asn Val Tyr Leu Thr Asp
1               5               10                  15
Ser Tyr Leu Lys Gly Val Ile Ser Phe Ser Glu Cys Asn Ala Leu Gly
        20              25              30
Ser Tyr Ile Phe Asn Gly Pro Tyr Leu Lys Asn Asp Tyr Thr Asn Leu
        35              40              45
Ile Ser Arg Gln Asn Pro Leu Ile Glu His Met Asn Leu Lys Lys Leu
    50              55              60
Asn Ile Thr Gln Ser Leu Ile Ser Lys Tyr His Lys Gly Glu Ile Lys
65              70              75              80
Leu Glu Glu Pro Thr Tyr Phe Gln Ser Leu Leu Met Thr Tyr Lys Ser
            85              90              95
Met Thr Ser Ser Glu Gln Ile Ala Thr Thr Asn Leu Leu Lys Lys Ile
        100             105             110
Ile Arg Arg Ala Ile Glu Ile Ser Asp Val Lys Val Tyr Ala Ile Leu
        115             120             125
Asn Lys Leu Gly Leu Lys Glu Lys Asp Lys Ile Lys Ser Asn Asn Gly
    130             135             140
Gln Asp Glu Asp Asn Ser Val Ile Thr Thr Ile Ile Lys Asp Asp Ile
145             150             155             160
Leu Ser Ala Val Lys Asp Asn Gln Ser His Leu Lys Ala Asp Lys Asn
            165             170             175
His Ser Thr Lys Gln Lys Asp Thr Ile Lys Thr Thr Leu Leu Lys Lys
        180             185             190
Leu Met Cys Ser Met Gln His Pro Pro Ser Trp Leu Ile His Trp Phe
        195             200             205
```

11

```
Asn Leu Tyr Thr Lys Leu Asn Asn Ile Leu Thr Gln Tyr Arg Ser Asn
    210                 215                 220
Glu Val Lys Asn His Gly Phe Thr Leu Ile Asp Asn Gln Thr Leu Ser
225                 230                 235                 240
Gly Phe Gln Phe Ile Leu Asn Gln Tyr Gly Cys Ile Val Tyr His Lys
                245                 250                 255
Glu Leu Lys Arg Ile Thr Val Thr Thr Tyr Asn Gln Phe Leu Thr Trp
                260                 265                 270
Lys Asp Ile Ser Leu Ser Arg Leu Asn Val Cys Leu Ile Thr Trp Ile
        275                 280                 285
Ser Asn Cys Leu Asn Thr Leu Asn Lys Ser Leu Gly Leu Arg Cys Gly
    290                 295                 300
Phe Asn Asn Val Ile Leu Thr Gln Leu Phe Leu Tyr Gly Asp Cys Ile
305                 310                 315                 320
Leu Lys Leu Phe His Asn Glu Gly Phe Tyr Ile Ile Lys Glu Val Glu
                325                 330                 335
Gly Phe Ile Met Ser Leu Ile Leu Asn Ile Thr Glu Glu Asp Gln Phe
                340                 345                 350
Arg Lys Arg Phe Tyr Asn Ser Met Leu Asn Asn Ile Thr Asp Ala Ala
        355                 360                 365
Asn Lys Ala Gln Lys Asn Leu Leu Ser Arg Val Cys His Thr Leu Leu
    370                 375                 380
Asp Lys Thr Val Ser Asp Asn Ile Ile Asn Gly Arg Trp Ile Ile Leu
385                 390                 395                 400
Leu Ser Lys Phe Leu Lys Leu Ile Lys Leu Ala Gly Asp Asn Asn Leu
                405                 410                 415
Asn Asn Leu Ser Glu Leu Tyr Phe Leu Phe Arg Ile Phe Gly His Pro
                420                 425                 430
Met Val Asp Glu Arg Gln Ala Met Asp Ala Val Lys Ile Asn Cys Asn
            435                 440                 445
Glu Thr Lys Phe Tyr Leu Leu Ser Ser Leu Ser Met Leu Arg Gly Ala
    450                 455                 460
Phe Ile Tyr Arg Ile Ile Lys Gly Phe Val Asn Asn Tyr Asn Arg Trp
465                 470                 475                 480
Pro Thr Leu Arg Asn Ala Ile Val Leu Pro Leu Arg Trp Leu Thr Tyr
                485                 490                 495
Tyr Lys Leu Asn Thr Tyr Pro Ser Leu Leu Glu Leu Thr Glu Arg Asp
            500                 505                 510
Leu Ile Val Leu Ser Gly Leu Arg Phe Tyr Arg Glu Phe Arg Leu Pro
            515                 520                 525
Lys Lys Val Asp Leu Glu Met Ile Ile Asn Asp Lys Ala Ile Ser Pro
    530                 535                 540
Pro Lys Asn Leu Ile Trp Thr Ser Phe Pro Arg Asn Tyr Met Pro Ser
545                 550                 555                 560
His Ile Gln Asn Tyr Ile Glu His Glu Lys Leu Lys Phe Ser Glu Ser
                565                 570                 575
Asp Lys Ser Arg Arg Val Leu Glu Tyr Tyr Leu Arg Asp Asn Lys Phe
            580                 585                 590
Asn Glu Cys Asp Leu Tyr Asn Cys Val Val Asn Gln Ser Tyr Leu Asn
        595                 600                 605
Asn Pro Asn His Val Val Ser Leu Thr Gly Lys Glu Arg Glu Leu Ser
    610                 615                 620
Val Gly Arg Met Phe Ala Met Gln Pro Gly Met Phe Arg Gln Val Gln
625                 630                 635                 640
Ile Leu Ala Glu Lys Met Ile Ala Glu Asn Ile Leu Gln Phe Phe Pro
                645                 650                 655
Glu Ser Leu Thr Arg Tyr Gly Asp Leu Glu Leu Gln Lys Ile Leu Glu
                660                 665                 670
```

12

```
Leu Lys Ala Gly Ile Ser Asn Lys Ser Asn Arg Tyr Asn Asp Asn Tyr
        675                 680                 685
Asn Asn Tyr Ile Ser Lys Cys Ser Ile Ile Thr Asp Leu Ser Lys Phe
        690                 695                 700
Asn Gln Ala Phe Arg Tyr Glu Thr Ser Cys Ile Cys Ser Asp Val Leu
705                 710                 715                 720
Asp Glu Leu His Gly Val Gln Ser Leu Phe Ser Trp Leu His Leu Thr
                725                 730                 735
Ile Pro His Val Thr Ile Ile Cys Thr Tyr Arg His Ala Pro Pro Tyr
                740                 745                 750
Ile Gly Asp His Ile Val Asp Leu Asn Asn Val Asp Glu Gln Ser Gly
                755                 760                 765
Leu Tyr Arg Tyr His Met Gly Gly Ile Glu Gly Trp Cys Gln Lys Leu
        770                 775                 780
Trp Thr Ile Glu Ala Ile Ser Leu Leu Asp Leu Ile Ser Leu Lys Gly
785                 790                 795                 800
Lys Phe Ser Ile Thr Ala Leu Ile Asn Gly Asp Asn Gln Ser Ile Asp
                805                 810                 815
Ile Ser Lys Pro Ile Arg Leu Met Glu Gly Gln Thr His Ala Gln Ala
                820                 825                 830
Asp Tyr Leu Leu Ala Leu Asn Ser Leu Lys Leu Leu Tyr Lys Glu Tyr
        835                 840                 845
Ala Gly Ile Gly His Lys Leu Lys Gly Thr Glu Thr Tyr Ile Ser Arg
        850                 855                 860
Asp Met Gln Phe Met Ser Lys Thr Ile Gln His Asn Gly Val Tyr Tyr
865                 870                 875                 880
Pro Ala Ser Ile Lys Lys Val Leu Arg Val Gly Pro Trp Ile Asn Thr
                885                 890                 895
Ile Leu Asp Asp Phe Lys Val Ser Leu Glu Ser Ile Gly Ser Leu Thr
                900                 905                 910
Gln Glu Leu Glu Tyr Arg Gly Glu Ser Leu Leu Cys Ser Leu Ile Phe
        915                 920                 925
Arg Asn Val Trp Leu Tyr Asn Gln Ile Ala Leu Gln Leu Lys Asn His
        930                 935                 940
Ala Leu Cys Asn Asn Lys Leu Tyr Leu Asp Ile Leu Lys Val Leu Lys
945                 950                 955                 960
His Leu Lys Thr Phe Phe Asn Leu Asp Asn Ile Asp Thr Ala Leu Thr
                965                 970                 975
Leu Tyr Met Asn Leu Pro Met Leu Phe Gly Gly Gly Asp Pro Asn Leu
                980                 985                 990
Leu Tyr Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu Thr Glu Ala
        995                 1000                1005
Ile Val His Ser Val Phe Ile Leu Ser Tyr Tyr Thr Asn His Asp Leu
        1010                1015                1020
Lys Asp Lys Leu Gln Asp Leu Ser Asp Asp Arg Leu Asn Lys Phe Leu
1025                1030                1035                1040
Thr Cys Ile Ile Thr Phe Asp Lys Asn Pro Asn Ala Glu Phe Val Thr
                1045                1050                1055
Leu Met Arg Asp Pro Gln Ala Leu Gly Ser Glu Arg Gln Ala Lys Ile
                1060                1065                1070
Thr Ser Glu Ile Asn Arg Leu Ala Val Thr Glu Val Leu Ser Thr Ala
        1075                1080                1085
Pro Asn Lys Ile Phe Ser Lys Ser Ala Gln His Tyr Thr Thr Thr Glu
        1090                1095                1100
Ile Asp Leu Asn Asp Ile Met Gln Asn Ile Glu Pro Thr Tyr Pro His
1105                1110                1115                1120
Gly Leu Arg Val Val Tyr Glu Ser Leu Pro Phe Tyr Lys Ala Glu Lys
                1125                1130                1135
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Ile Val Asn Leu Ile Ser Gly Thr Lys Ser Ile Thr Asn Ile Leu Glu
          1140                1145                1150
Lys Thr Ser Ala Ile Asp Leu Thr Asp Ile Asp Arg Ala Thr Glu Met
          1155                1160                1165
Met Arg Lys Asn Ile Thr Leu Leu Ile Arg Ile Leu Pro Leu Asp Cys
     1170                1175                1180
Asn Arg Asp Lys Arg Glu Ile Leu Ser Met Glu Asn Leu Ser Ile Thr
1185                1190                1195                1200
Glu Leu Ser Lys Tyr Val Arg Glu Arg Ser Trp Ser Leu Ser Asn Ile
          1205                1210                1215
Val Gly Val Thr Ser Pro Ser Ile Met Tyr Thr Met Asp Ile Lys Tyr
          1220                1225                1230
Thr Thr Ser Thr Ile Ser Ser Gly Ile Ile Ile Glu Lys Tyr Asn Val
          1235                1240                1245
Asn Ser Leu Thr Arg Gly Glu Arg Gly Pro Thr Lys Pro Trp Val Gly
          1250                1255                1260
Ser Ser Thr Gln Glu Lys Lys Thr Met Pro Val Tyr Asn Arg Gln Val
1265                1270                1275                1280
Leu Thr Lys Lys Gln Arg Asp Gln Ile Asp Leu Leu Ala Lys Leu Asp
          1285                1290                1295
Trp Val Tyr Ala Ser Ile Asp Asn Lys Asp Glu Phe Met Glu Glu Leu
          1300                1305                1310
Ser Ile Gly Thr Leu Gly Leu Thr Tyr Glu Lys Ala Lys Lys Leu Phe
          1315                1320                1325
Pro Gln Tyr Leu Ser Val Asn Tyr Leu His Arg Leu Thr Val Ser Ser
     1330                1335                1340
Arg Pro Cys Glu Phe Pro Ala Ser Ile Pro Ala Tyr Arg Thr Thr Asn
1345                1350                1355                1360
Tyr His Phe Asp Thr Ser Pro Ile Asn Arg Ile Leu Thr Glu Lys Tyr
          1365                1370                1375
Gly Asp Glu Asp Ile Asp Ile Val Phe Gln Asn Cys Ile Ser Phe Gly
          1380                1385                1390
Leu Ser Leu Met Ser Val Val Glu Gln Phe Thr Asn Val Cys Pro Asn
          1395                1400                1405
Arg Ile Ile Leu Ile Pro Lys Leu Asn Glu Ile His Leu Met Lys Pro
     1410                1415                1420
Pro Ile Phe Thr Gly Asp Val Asp Ile His Lys Leu Lys Gln Val Ile
1425                1430                1435                1440
Gln Lys Gln His Met Phe Leu Pro Asp Lys Ile Ser Leu Thr Gln Tyr
          1445                1450                1455
Val Glu Leu Phe Leu Ser Asn Lys Thr Leu Lys Ser Gly Ser His Val
          1460                1465                1470
Asn Ser Asn Leu Ile Leu Ala His Lys Ile Ser Asp Tyr Phe His Asn
          1475                1480                1485
Thr Tyr Ile Leu Ser Thr Asn Leu Ala Gly His Trp Ile Leu Ile Ile
          1490                1495                1500
Gln Leu Met Lys Asp Ser Lys Gly Ile Phe Glu Lys Asp Trp Gly Glu
1505                1510                1515                1520
Gly Tyr Ile Thr Asp His Met Phe Ile Asn Leu Lys Val Phe Phe Asn
          1525                1530                1535
Ala Tyr Lys Thr Tyr Leu Leu Cys Phe His Lys Gly Tyr Gly Lys Ala
          1540                1545                1550
Lys Leu Glu Cys Asp Met Asn Thr Ser Asp Leu Leu Cys Val Leu Glu
          1555                1560                1565
Leu Ile Asp Ser Ser Tyr Trp Lys Ser Met Ser Lys Val Phe Leu Glu
          1570                1575                1580
Gln Lys Val Ile Lys Tyr Ile Leu Ser Gln Asp Ala Ser Leu His Arg
1585                1590                1595                1600
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Val Lys Gly Cys His Ser Phe Lys Leu Trp Phe Leu Lys Arg Leu Asn
              1605                1610                1615
Val Ala Glu Phe Thr Val Cys Pro Trp Val Val Asn Ile Asp Tyr His
              1620                1625                1630
Pro Thr His Met Lys Ala Ile Leu Thr Tyr Ile Asp Leu Val Arg Met
              1635                1640                1645
Gly Leu Ile Asn Ile Asp Arg Ile His Ile Lys Asn Lys His Lys Phe
          1650                1655                1660
Asn Asp Glu Phe Tyr Thr Ser Asn Leu Phe Tyr Ile Asn Tyr Asn Phe
1665                1670                1675                1680
Ser Asp Asn Thr His Leu Leu Thr Lys His Ile Arg Ile Ala Asn Ser
              1685                1690                1695
Glu Leu Glu Asn Asn Tyr Asn Lys Leu Tyr His Pro Thr Pro Glu Thr
              1700                1705                1710
Leu Glu Asn Ile Leu Ala Asn Pro Ile Lys Ser Asn Asp Lys Lys Thr
          1715                1720                1725
Leu Asn Asp Tyr Cys Ile Gly Lys Asn Val Asp Ser Ile Met Leu Pro
          1730                1735                1740
Leu Leu Ser Asn Lys Lys Leu Ile Lys Ser Ser Ala Met Ile Arg Thr
1745                1750                1755                1760
Asn Tyr Ser Lys Gln Asp Leu Tyr Asn Leu Phe Pro Met Val Val Ile
              1765                1770                1775
Asp Arg Ile Ile Asp His Ser Gly Asn Thr Ala Lys Ser Asn Gln Leu
          1780                1785                1790
Tyr Thr Thr Thr Ser His Gln Ile Ser Leu Val His Asn Ser Thr Ser
          1795                1800                1805
Leu Tyr Cys Met Leu Pro Trp His His Ile Asn Arg Phe Asn Phe Val
     1810                1815                1820
Phe Ser Ser Thr Gly Cys Lys Ile Ser Ile Glu Tyr Ile Leu Lys Asp
1825                1830                1835                1840
Leu Lys Ile Lys Asp Pro Asn Cys Ile Ala Phe Ile Gly Glu Gly Ala
              1845                1850                1855
Gly Asn Leu Leu Leu Arg Thr Val Val Glu Leu His Pro Asp Ile Arg
          1860                1865                1870
Tyr Ile Tyr Arg Ser Leu Lys Asp Cys Asn Asp His Ser Leu Pro Ile
          1875                1880                1885
Glu Phe Leu Arg Leu Tyr Asn Gly His Ile Asn Ile Asp Tyr Gly Glu
     1890                1895                1900
Asn Leu Thr Ile Pro Ala Thr Asp Ala Thr Asn Asn Ile His Trp Ser
1905                1910                1915                1920
Tyr Leu His Ile Lys Phe Ala Glu Pro Ile Ser Leu Phe Val Cys Asp
              1925                1930                1935
Ala Glu Leu Ser Val Thr Val Asn Trp Ser Lys Ile Ile Ile Glu Trp
          1940                1945                1950
Ser Lys His Val Arg Lys Cys Lys Tyr Cys Ser Ser Val Asn Lys Cys
          1955                1960                1965
Met Leu Ile Val Lys Tyr His Ala Gln Asp Asp Ile Asp Phe Lys Leu
     1970                1975                1980
Asp Asn Ile Thr Ile Leu Lys Thr Tyr Val Cys Leu Gly Ser Lys Leu
1985                1990                1995                2000
Lys Gly Ser Glu Val Tyr Leu Val Leu Thr Ile Gly Pro Ala Asn Ile
              2005                2010                2015
Phe Pro Val Phe Asn Val Val Gln Asn Ala Lys Leu Ile Leu Ser Arg
          2020                2025                2030
Thr Lys Asn Phe Ile Met Pro Lys Lys Ala Asp Lys Glu Ser Ile Asp
          2035                2040                2045
Ala Asn Ile Lys Ser Leu Ile Pro Phe Leu Cys Tyr Pro Ile Thr Lys
     2050                2055                2060
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Lys Gly Ile Asn Thr Ala Leu Ser Lys Leu Lys Ser Val Val Ser Gly
2065                2070                2075                2080
Asp Ile Leu Ser Tyr Ser Ile Ala Gly Arg Asn Glu Val Phe Ser Asn
                2085                2090                2095
Lys Leu Ile Asn His Lys His Met Asn Ile Leu Lys Trp Phe Asn His
                2100                2105                2110
Val Leu Asn Phe Arg Ser Thr Glu Leu Asn Tyr Asn His Leu Tyr Met
                2115                2120                2125
Val Glu Ser Thr Tyr Pro Tyr Leu Ser Glu Leu Leu Asn Ser Leu Thr
    2130                2135                2140
Thr Asn Glu Leu Lys Lys Leu Ile Lys Ile Thr Gly Ser Leu Leu Tyr
2145                2150                2155                2160
Asn Phe His Asn Glu
                2165


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18

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